REMARKS

Claims 1-6, 8-9, 11, and 14-15 are presently pending in the captioned application. The amendments are presented in the expectation that the amendments will place this application in condition for allowance. The amendments were made to place the limitations of dependent claim 7 in independent claim 1. The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of claims 1-9, 11, 14, and 15 under 35 U.S.C. § 103

The Office Action states that claims 1-9, 11, 14, and 15 are rejected under 35 U.S.C. § 103 as being obvious. The Office Action rejects claims 1, 2, 5-9, 11, and 14 over Nath et al. (Novel Met-Enkephalin Analogue, Pharm. Res. Vol. 31, No. 5, pages 269-273 (1995)) in view of Chiesi et al. (U.S. Patent No. 5,855,916); claims 1-3, 7-9, and 11 over European Patent Application No. 0 463 653 ("'653") in view of Nath et al.; claims 1, 2, 4, 7-9, 11, and 14 over Hora et al. (U.S. Patent No. 5,977,856) in view of Nath et al.; and claims 1, 7-9, 11, and 15 over French Patent 2 710 268 ("'268") in view of Nath et al.

Applicants respectfully traverse this rejection because all three prongs for a *prima facie* case of obviousness have not been established for each of the rejections. Specifically, all the

claim limitations are not present in the cited references and one of ordinary skill in the art would have had no motivation to modify the cited references into the present invention.

To establish a *prima facie* case of obviousness, the Examiner must establish: (1) that some suggestion or motivation to modify the references exists; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all the claim limitations. In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The Examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

1. Rejection of claims 1, 2, 5-9, 11 and 14 over Nath et al. in view of Chiesi et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 5-9, 11, and 14 are rejected under 103 U.S.C. 103(a) as being obvious over the Nath et al article in view of Chiesi et al. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. The Nath et al article does not teach the opioid peptide in combination with a cyclodextrin derivative. Chiesi et al teach forming an

inclusion complex of a basic drug and a cyclodextrin such as hydroxypropyl-β-cyclodextrin and dimethyl-β-cyclodextrin. The inclusion complex results in improved storage stability and enhanced water solubility and bioavailabilty for the drug. The drug is to be administered orally or parenterally. See, e.g. column 3, lines 15-21; column 8, lines 54-56; and claim 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to combine the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al in order to form inclusion complexes for pharmaceutical administration because the opioid peptide of the Nath et al article is a basic drug as required by Chiesi et al and because combining the opioid peptide of the Nath et al article with the cyclodextrins of Chiesi et al would have been expected to increase the solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and cyclodextrin derivative in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicant's arguments filed December 24, 2002 have been fully considered but they are not persuasive.

The examiner maintains his positions for the reasons of record in this application, and especially for the reasons set forth in section 8 of the Office action mailed June 25, 2002.

With respect to the rejection based upon the combination of the Nath et al article and Chiesi et al, Applicants argue that the "consisting essentially of" terminology in the instant clams excludes the acid which is required by Chiesi et al. The examiner reiterates that the issue is not whether the additional ingredient is critical to the prior art composition, but rather is whether the additional ingredient materially affects the basic and novel characteristics of Applicants' claimed compositions. Applicants' specification, e.g., at page 5, lines 2-3, recites that increased water solubility is a goal of Applicants. An ingredient which is disclosed by the prior art (i.e. the acid of Chiese et al) as helping to achieve this goal of Applicants does not materially affect the basic and novel characteristic of

> Applicants' claimed compositions. Applicants argue that the "consisting essentially of" terminology excludes even those additional ingredients which positively affect the characteristics of Applicants' invention (see page 9, lines 7-10, and page 10, 11-12, of the response). However, the examiner could not find any support for this argument in any of the cited cases, and Applicant are requested more specifically to point the support for this position so that the examiner can more fully respond to the argument. In any event, the argument that the "consisting essentially of" excludes any additional components which have "some effect on a basic characteristic of the invention" can not be accepted, because any ingredient will inherently have "some" effect on a basic characteristic of an invention, and Applicants' argument would in effect reduce "consisting essentially of" language to "consisting of" language. The arguments that there is no motivation to modify the Nath et al article because the peptide is already soluble in water and stable, and that there is no reasonable expectations of success in forming orally available inclusion complexes, are addressed at page 6, last paragraph through page 7 of the Office action mailed June 25, 2002.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

The presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. teach the compound Tyr-D-Ala-Gly-MePhe-Gly-NHC_3H_7. Nath et al. do not disclose inclusion complexes

containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5 to 2:1, as required by the presently pending claims. Accordingly, Nath et al do not teach each and every limitation of independent claim 1.

Chiesi et al. do not remedy these deficiencies. Chiesi et al. disclose multicomponent inclusion complexes containing a basic-type drug, a cyclodextrin, and an acid as the essential components. Chiesi et al. teach that the acid is the critical component to establishing the water solubility of the inclusion complexes. In fact, Chiesi et al. specifically disclose "the present invention relates to the use of an acid in the preparation of complexes with a cyclodextrin...with the purpose of increasing the water solubility of the cyclodextrin itself." (See column 2, lines 8-12). Chiesi et al. provide no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the basic-type drugs used in the disclosed inclusion complexes. Additionally, Chiesi et al. provide no teaching for inclusion complexes that do not contain an acid as an essential component.

Applicants' claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative as the only essential components in a molar ratio of 1:5 to 2:1. Neither reference cited by the Examiner teaches inclusion

complexes having only these two essential components in the specified molar ratio. As shown above, Nath et al. merely teach a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, Chiesi et al. teach inclusion complexes which require a basic-type drug, a cyclodextrin derivative, and an acid. The acid is a critical component of the inclusion complexes taught by Chiesi et al. since Chiesi et al. disclose that the acid itself provides the desired increase in water solubility. In contrast, the presently claimed inclusion complexes do not contain an acid to increase water solubility.

The transition phrase "consisting essentially of" is commonly used to signal a partially open claim in a patent. PPG Industries Inc. v. Guardian Industries Corp., 48 USPQ2d 1351, 1353 (Fed. Cir. 1998). Use of this transitional phrase in a claim indicates the claim necessarily includes the listed ingredients and "is open to unlisted ingredients that do not materially affect the basic and novel properties of the invention." Id. at 1353-54. An unlisted ingredient has a material effect on the characteristics of the invention if the effect is of importance or of consequence to those of ordinary skill in the relevant art. Id. at 1354. "Consisting essentially of" excludes the addition of another ingredient that materially affects the characteristics of the invention. Water Technologies Corp. v. Calco Ltd., 7 USPQ2d 1097, 1102 (Fed. Cir. 1988); Reese v. Hurst, 211 USPQ 936, 943 (C.C.P.A. 1981); In re

Garnero, 162 USPQ 221, 223 (C.C.P.A. 1969).

The basic and novel characteristic of the presently claimed invention relates to an inclusion complex effective for oral administration (i.e. water soluble) based solely on a molar ratio of 1:5 to 2:1 of a specific opioid peptide and a cyclodextrin derivative. The use of the transitional phrase "consisting essentially of" excludes any additional components in the inclusion complex that materially affect this basic and novel characteristic as per In re Garnero, holding that "In either event it cannot be said that the additional ingredient would not materially affect the basic and novel characteristic of appellant's product which is that the perlite particles are held together without any additional material." 162 USPQ at 223. Contrary to the Examiner's assertion, such use of the "consisting essentially of" terminology would not "in effect reduce 'consisting essentially of' language to 'consisting of' language", especially in view of the fact that the component at issue (the acid component of Chiesi et al.) is taught for the specific purpose of enhancing water-solubility, and thus oral efficacy, of the disclosed inclusion complexes. As applicants have shown, this is the exact situation that the "consisting essentially of" terminology is intended to avoid.

Further, the Examiner has admitted on the record that water solubility is a basic property of the claimed invention, stating the alleged combination "would have been expected to increase the

solubility and bioavailability of the opioid peptides, a result which is desirable for pharmaceutical agents." Further, the Chiesi et al. reference explicitly sates "the present invention relates to the use of an acid...with the purpose of increasing the water solubility of the cyclodextrin itself." Clearly, this effect would be "of importance or of consequence to those of ordinary skill in the relevant art." Accordingly, the Chiesi et al. reference on its face demonstrates that the acid component materially effects the water solubility of the inclusion complexes, i.e. a characteristic of the claimed invention. It does not matter whether this is a positive or a negative effect; all that is necessary to avoid inclusion of this unrecited element in a claim reciting the "consisting essentially of" transition phrase is that the element have some effect on a basic characteristic of the invention.

Additionally, a person of ordinary skill in the art would recognize that the opioid peptide used according to the presently claimed invention is already soluble in water and stable. Accordingly, this peptide does not require improved water solubility or stability. The presently claimed invention, then, is patentably distinct from the references cited by the Examiner. A person of ordinary skill in the art would have had no reasonable expectation of success in forming orally available inclusion complexes containing only the presently claimed specific peptide as well as a cyclodextrin, without an additional acid, as required by

Amgen, Inc. v. Chugai Pharm. Co..

Applicants additionally provide below further data showing that the opioid peptide to cyclodextrin derivative molar ratio of 1:5 to 2:1 is essential for the biological activity of the presently claimed inclusion complexes by the oral route. This data shows that it would not at all have been obvious that a cyclodextrin derivative enhances the stability, solubility, and bioavailability of opioid peptides delivered orally.

Comparative analgesic activity by oral route of the beta cyclodextrin complexes (1:1 and 1:2)

Dose (mg/kg)	**% analgesic activity**
Peptide:beta cyclodextrin complexes (1:1)	
10	100
7.5	80
5.0	60
2.5	40
1.25	20
Peptide:beta cyclodextrin complexes (1:2)	
7.5	100
5.0	90
3.5	70
2.5	60
1.25	20
0.625	10

Complex	**ED90 (mg/kg)**	**ED50 (mg/kg)**
Peptide:beta cyclodextrin complexes (1:1)	13.8445	3.3157
Peptide:beta cyclodextrin complexes (1:2)	6.0928	2.1280

In view of this data, it would not at all have been obvious, based on the teachings of Nath et al. in combination with Chiesi et al.,

that the cyclodextrin derivative in presently claimed inventive inclusion complexes enhances the stability, solubility, and bioavailability of the opioid peptides delivered orally.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Chiesi et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 5-6, 8-9, 11, and 14.

2. Rejection of claims 1-3, 7-9, and 11 over EP '653 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1-3, 7-9, and 11 are rejected under 103 U.S.C. 103(a) as being obvious over the European Patent Application '653 in view of the Nath et al article. The European Patent Application '653 teaches combining drugs, including peptide drugs such as enkephalins, with cyclodextrins, especially B-cyclodextrin. The combination permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs. See, e.g., column 1, lines 8-24; column 4, lines 4-11; and column 5, lines 31-36. The European Patent Application '653 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-Ala-Gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. See, e.g., the Abstract and page 269, column 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of the European Patent Application '653 because the opioid peptide of the Nath et al article is a specific known example of the peptide and enkephalin drugs which are contemplated by the European Patent Application '653 and because administering the opioid peptide of Nath et

al nasally in the pharmaceutical formulations of the European Patent Application '653 would avoid problems of poor absorption after oral administration and of undesirable metabolism as taught by the European Patent Application '653. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above-outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicant's arguments filed December 24, 2002 have been fully considered but they are not persuasive.

The examiner maintains his positions for the reasons of record in this application, and especially for the reasons set forth in section 8 of the Office action mailed June 25, 2002.

The rejection based upon the combination of the European Patent Application '653 and the Nath et al article set forth in the previous Office action is maintained. For those reasons analogous to those set forth above with respect to Chiesi et al's enhancers, the absorption enhancers of the European Patent Application '653 are not excluded by Applicants' "consisting essentially of" terminology. The examiner disagrees with Applicants' summary of the claimed invention set forth at page 16, lines 5-7, of the response. Method claim 11 only recites administering the compositions, and does not require oral administration. Method claim 15, also dependent upon independent composition claim 1, specifically recites topical administration. The prior art need not suggest oral administration in order to establish prima facie obviousness of Applicant's composition claims, or to establish obviousness of those method claims which do not specify oral administration. Applicants argue that the compositions of the European Patent Application '653 are not orally efficacious. This argument is contradicted by the disclosure of the European Patent Application '653 at column 7, lines 16-17. In any event, a statement in the background of the invention concerning the oral administration of a drug per se (the examiner assumes that Applicants are referring to column 1, lines 11-15, of the European Patent Application '653) is not the

> equivalent of a statement that the inventive compositions of the European Patent Application '653 themselves are not orally efficacious. Applicants argue that the European Patent Application '653 does not disclose either the claimed specific opioid peptide itself or any other modification of enkephalin molecules. The examiner agrees; however, as the rejection is not an anticipation rejection but rather is an obviousness rejection based upon a combination of references, the argument is not convincing. As to the lack of any "practical demonstrations" regarding the disclosed drugs in the European Patent Application '653, such demonstrations, examples, etc. are not a requirement to apply a reference under 35 U.S.C. 102 and/or 103. See MPEP 2121 and 2121.02 as to the issue of enablement and references applied under 35 U.S.C. 103.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5 to 2:1, as required by the presently pending claims. Accordingly,

each and every limitation of independent claim 1 is not taught by Nath et al.

EP '653 does not remedy these deficiencies. EP '653 teaches combining drugs including peptide drugs such as enkephalins with an enhancer of absorption at a mucosal surface and a cyclodextrin. The reference further teaches that undesirable side-effects due to using an absorption enhancer alone may be avoided when an absorption enhancer is used in combination with a cyclodextrin to permit nasal administration. See Column 3, lines 9-15.

Further, as noted by the Examiner, the combination disclosed by EP '653 "permits the drugs to be administered nasally, thereby avoiding the problems of poor absorption after oral administration and avoiding undesirable metabolism of the drugs." Accordingly, as the Examiner has admitted on the record, the combinations disclosed by EP '653 are preferably administered nasally since they show poor oral efficacy.

Additionally, EP '653 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed medicaments. Further, the absorption enhancers are necessary to increase the permeability of the nasal mucosa in order to enable the disclosed intranasal administration. See column 1,

lines 52-58.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy that are orally efficacious, rather than preferably administered intranasally. Accordingly, the presently claimed invention is entirely different from the EP '653 diclosure, relating to nasal administration of cyclodextrin to avoid the problems of poor absorption after oral administration and to avoid undesirable metabolism of drugs.

Additionally, as presented above in section 1, the arguments of which are hereby incorporated by reference in their entirety, applicants have provided further data showing that the claimed opioid peptide to cyclodextrin derivative molar ratio of 1:5 to 2:1 is essential for the biological activity of the presently claimed inclusion complexes by the oral route. This data shows that it would not at all have been obvious in view of the EP '653 and Nath et al. references that a cyclodextrin derivative enhances the stability, solubility, and bioavailability of opioid peptides delivered orally.

The opioid peptides included in the presently claimed inclusion complexes, then, are effective by oral administration, a significant improvement over the teachings of the EP '653

reference. The data in Tables 2 and 3 of the instant specification, at pages 14 and 15, further support this assertion by demonstrating that the presently claimed inclusion complexes are effective via oral administration. A person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that EP '653 teaches away from the presently claimed invention requiring a composition which is orally efficacious.

Further, applicants claims as presently amended are limited to inclusion complexes containing an opioid peptide and a cyclodextrin derivative in a molar ratio of 1:5 to 2:1, as the only essential components. Neither reference cited by the Examiner teaches inclusion complexes having only these two essential components. As shown above, Nath et al. merely teaches a particular compound by itself, without inclusion of a cyclodextrin derivative. Likewise, EP '653 teaches inclusion complexes which require a peptide drug, a cyclodextrin derivative, and an enhancer of absorption at a mucosal surface. The absorption enhancer is a critical component of the inclusion complexes taught by EP '653 since they are necessary for the enablement of the intranasal administration. In contrast, the presently claimed inclusion complexes do not contain an absorption

enhancer.

The Examiner has submitted it is necessary for applicants to submit evidence showing that the "consisting essentially of" language in the present claims excludes the absorption enhancers shown by EP '653 as a component which materially affects the basic and novel characteristics of the claimed composition. This is unnecessary in the present case, however, as the EP '653 reference on its face demonstrates that the absorption enhancers materially effect the characteristics of the claimed invention, i.e. by enabling them to be used for intranasal administration.

Clearly, the mode of administration is a critical and novel feature of the presently claimed invention, as discussed above. Accordingly, the use of an absorption enhancer as disclosed by EP '653 to make the compositions effective for intranasal administration is "of importance or of consequence to those of ordinary skill in the relevant art" and affects the basic and novel characteristics of the presently claimed invention. The presently claimed invention, then, is patentably distinct from the references cited by the Examiner.

Further, applicants note that although EP '653 states that any active drug substance may be used in the disclosed compositions, only drugs such as proteins and peptides such as insulin,

gentamicin, glucagon, growth hormone, calcitonins and synthetic modifications thereof, enkephalins, interferons, etc. are specifically exemplified. However, EP '653 specifically discloses neither the presently claimed specific opioid peptide itself nor any other synthetic modification of enkephalin molecules.

Further, while EP '653 does provide an example of a cyclodextrin complex with Laureth-9 and states that any active drug substance may be used in the embodied cmpositions, the reference does not actually provide any practical demonstrations, in the form of Examples or otherwise, regarding the disclosed drugs. Accordingly, this reference is non-enabling for the combination asserted by the Examiner. In re Wiggins, 179 USPQ 421, 425 (C.C.P.A. 1973).

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of EP '653 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1-3, 8-9, and 11.

3. Rejection of claims 1, 2, 4, 7-9, 11, and 14 are rejected over Hora et al. in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 2, 4, 7-9, 11, and 14 are rejected under 35 U.S.C. 103(a) as being obvious over Hora et al in view of the Nath et al article. Hora et al teach combining polypeptide drugs with cyclodextrins, B-cyclodextrin,

including hydroxyethyl-B-cyclodextrin. The combination improves the solubility and the stability of polypeptide drugs, and permits oral administration as well. . . . Hora et al do not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulations of Hora et al because the opioid peptide of the Nath et al article is a specific known example of the polypeptide drugs which are contemplated by Hora et al and because administering the opioid peptide of Nath et al in the pharmaceutical formulations of Hora et al. would improve the solubility and the stability of the opioid peptide as taught by Hora et al. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above- outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicant's arguments filed December 24, 2002 have been fully considered but they are not persuasive.

The examiner maintains his positions for the reasons of record in this application, and especially for the reasons set forth in section 8 of the Office action mailed June 25, 2002.

The rejection based upon the combination of Hora et al and the Nath et al article set forth in the previous Office action is maintained. Applicants argue that inclusion complexes are not formed in the compositions of Hora. The examiner does not agree. A specific example of Hora et al indicates that inclusion complexes are formed between its polypeptides and its cyclodextrin derivatives (see column 25, lines 3-6). Further, the examiner does not agree that any special conditions are required to form inclusion complexes involving cyclodextrins. Hora et al's specification at column 7, lines 52-61, and at column 25, lines 3-6, indicates that mere mixing is sufficient to form inclusion complexes.

> Concerning Applicants' argument with respect to peptide:cyclodextrin ratio, see page 8, first paragraph, of the previous Office action. Concerning Applicants' argument at page 24, first full paragraph, of the response, the word "most" does not occur anywhere in the cited section of Hora et al. Further, this section of Hora et al's discloses can not be taken out of context to contradict the purpose of Hora et al's invention (see, e.g., the Title, the Abstract, and column 19, lines 51-58; see also the work "However" at claim 19, line 51, which distinguishes Hora et al's invention from the preceding discussion of untried agents). The statement in Hora et al relied upon by Applicants applies to untried agents, not to those tried and claimed by Hora et al.

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5 to 2:1, as required by the presently pending claims. Accordingly,

each and every limitation of independent claim 1 is not taught by Nath et al.

Hora et al. do not remedy these deficiencies. Hora et al. disclose a method and compositions for stabilizing and/or solubilizing polypeptide drugs by means of a cyclodextrin to obtain improved solubility and stability of the polypeptide drugs. This is achieved by combining the polypeptide with an effective solubilizing and/or stabilizing amount of a cyclodextrin, i.e. placing the polypeptide in an aqueous solution of the cyclodextrin. Accordingly, the polypeptide merely exists within the cyclodextrin aqueous solution; no reaction occurs between the cyclodextrin and the polypeptide-each exists as a separate component. Applicants note in this regard the Examiner's comments that "column 25, lines 3-6, indicates that mere mixing is sufficient to form inclusion complexes"; however, the teachings of the indicated passage that the cyclodextrin "may be added" to form a complex is hardly a sufficient enabling disclosure of the presently claimed inclusion complexes.

Further, Hora et al. provide no teaching that opioid peptides, such as the specific opioid peptide according to the presently claimed invention, are included among the polypeptide drugs used in the disclosed combinations.

In contrast, the presently claimed invention relates to inclusion complexes consisting essentially of a specific opioid peptide combined with a cyclodextrin derivative in a molar ratio of 1:5 to 2:1. Since the invention relates to inclusion complexes, it is inherent that the two components making up the complexes must react in some way to from the complexes. Accordingly, the resultant complexes represent an entirely new chemical entity as compared to the initial two components, sometimes even having a slight modification in the structure of these components in order to permit the inclusion complexes to be formed. Such complexes are neither disclosed nor even contemplated by the Hora et al. reference, which merely shows placing a polypeptide in an aqueous cyclodextrin solution. Since Hora et al. does not contemplate the use of both of the presently claimed starting components, the disclosure of Hora et al. cannot recognize the unique inclusion complexes that are presently claimed.

Further, applicants have observed that the peptide L-Tyr-D-Ala-Gly-N-methylphenylalanyl-glycyl-isopropylamide combined with beta-cyclodextrin in a 1:2 ratio is more effective orally than a 1:1 ratio. In fact, as presented above in section 1, the arguments of which are hereby incorporated by reference in their entirety, applicants have provided further data showing that the claimed

opioid peptide to cyclodextrin derivative molar ratio of 1:2 is more effective orally than a 1:1 ratio. This data shows that it would not at all have been obvious in view of the Hora et al. and Nath et al. references that a cyclodextrin derivative enhances the stability, solubility, and bioavailability of opioid peptides delivered orally when used in the claimed ratio.

Further, in the case of transdermal delivery, the effectiveness of these complexes is reversed. Accordingly, the molar ratio of peptide to cyclodextrin is not "routinely determined and optimized by one skill in the art" as the Examiner alleges. Formation of the presently claimed inclusion complexes containing this specific opioid peptide and a cyclodextrin would not have been obvious to a person of ordinary skill in the art without some teaching in this direction by the cited references. Neither reference cited by the Examiner contains such a teaching. Accordingly, the references cited by the Examiner merely provide an invitation to experiment. These references do not predict that any drug can be combined with cyclodextrins to form orally effective pharmaceutical compositions, nor do they teach how opioid peptides will behave when combined with cyclodextrins.

Accordingly, a person of ordinary skill in the art would have had no motivation to combine these references to arrive at the

presently claimed invention without impermissible hindsight. See In re Dembiczak, 50 USPQ2d 1614 (Fed. Cir. 1999). The presently claimed complexes were not achieved or suggested by the prior art given that the varying parameters and innumerable possibilities that would have had to be tried until the successful combination was arrived at. Since the prior art does not indicate which parameters are critical, or how the opioid can be expected to behave with cyclodextrin, the only direction as to which of the many choices is likely to be successful is impermissibly provided by the present application. "When a rejection depends on a combination of prior art references there must be some teaching, suggestion, or motivation to combine these references." In re Rouffet, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). As stated herein, no such motivation is present in the cited references.

Regarding the Examiner's assertion that "Hora et al's description of the cyclodextrins as stabilizing polypeptides in order to maintain their activity...is synonymous with Applicants' desired results of long duration of activity and improved efficacy", this is incorrect. In particular, while the portion of the reference cited by the Examiner does relate to stabilizing polypeptides, it does not disclose that such stabilization is performed in order to maintain the polypeptides activity. In fact,

column 19, lines 48-50 implies that most solubilization/stabilization agents provide an "appreciable loss of activity" to the polypeptides which are being stabilized. Accordingly, Hora et al.'s description of the cyclodextrins as stabilizing polypeptides is not actually synonymous with applicant's claimed inclusion complexes having a prolonged activity.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of Hora et al. and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 2, 4, 8-9, 11, and 14.

4. Rejection of claims 1, 7-12, and 15 are rejected over French Patent '268 in view of Nath et al.

As a basis for the rejection the Office Action states:

> Claims 1, 7-9, 11, and 15 are rejected under 35 U.S.C. 103(a) as being obvious over the French Patent '268 in view of the Nath et al article. The French Patent '268 teaches combining drugs, including analgesics and peptide hormones, with B-cyclodextrin. The combination permits the drugs to be administered transcutaneously. See the attached abstract. The French patent '268 does not teach administration of Applicants' particular opioid peptide. The Nath et al article teaches the highly active opioid peptide L-Tyr-D-ala-gly-NMe-Phe-Gly-NHC_3H_7. The opioid peptide can be administered orally or i.p. . . . It would have been obvious to one of ordinary skill in the art to at the time Applicants' invention was made to administer the opioid peptide of the Nath et al article in the pharmaceutical formulation of French Patent '268 because

the opioid peptide of the Nath et al article is a specific known example of the analgesic drugs which are contemplated by the French patent '268, because the French patent '268 would have been expected to be useful in transcutaneously administering polypeptides such as the opioid peptide of the Nath et al article because of the French Patent '268's disclosed ability to administer polypeptide hormones, and because administering the opioid peptide of Nath et al transcutaneously in the pharmaceutical formulations of the French Patent '268 would avoid problems of poor absorption after oral administration or of intrusive i.p. administration methods. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal ratios of opioid peptide and β-cyclodextrin in the above outlined compositions because component proportion is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical art.

Applicant's arguments filed December 24, 2002 have been fully considered but they are not persuasive.

The examiner maintains his positions for the reasons of record in this application, and especially for the reasons set forth in section 8 of the Office action mailed June 25, 2002.

The rejection based upon the combination of the French Patent '268 and the Nath et al article set forth in the previous Office action is maintained. As noted above, instant claim 11 does not require oral administration, and instant claim 15 positively recites topical administration. Accordingly, Applicants' arguments which are based upon the distinction between oral administration and transcutaneous administration are not convincing. As has been argued by the examiner, the rationale to combine references under 35 U.S.C. 103 need not be the same as Applicants' rationale. Accordingly, even if the motivation is based upon the desirability of forming transcutaneously administrable compositions, as long as the same composition as is claimed by Applicants is suggested, prima facie obviousness is established. The Examiner does not agree that the French Patent '268's disclosure of transcutaneous administration shows that the reference's compositions are not orally efficacious.

> This disclosure of the French Patent '268 only means that oral administration of the compositions has not been considered. There is no evidence of record that the compositions of the French Patent '268 are not orally efficacious. Again, the implication of the French Patent '268 that individual drugs per se are difficult to administer orally or are ineffective when administered orally does not mean that compositions comprising the drug are difficult to administer orally. Compositions comprising drugs have different pharmaceutical properties than the drugs per so. In re Fine, cited by Applicants, does not contradict MPEP 2144. under "Rationale Different From Applicant's Is Permissible".

Applicants respectfully traverse this rejection. The cited references, taken alone or in combination, do not teach each and every limitation of the presently claimed invention.

As stated above, the presently claimed invention relates to novel inclusion complexes consisting essentially of an opioid peptide of L-Tyrosyl-D-alanyl-glycyl-N-methylphenylalanyl-glycyl-isopropylamide and a cyclodextrin derivative as the sole essential components in a molar ratio of 1:5 to 2:1. These complexes are orally efficacious and prolong the duration of action of the active agent.

In contrast, Nath et al. do not disclose inclusion complexes containing the embodied compound in combination with a cyclodextrin derivative, let alone inclusion complexes in a molar ratio of 1:5 to 2:1, as required by the presently pending claims. Accordingly, each and every limitation of independent claim 1 is not taught by

Nath et al.

FR '268 does not remedy these deficiencies. FR '268 teaches combining various peptide hormones with a cyclodextrin. This combination permits the drugs to be administered transcutaneously. Indeed, as the Examiner has admitted, FR '268 teaches that transcutaneous administration is used as an alternative to oral administration to "avoid problems of poor absorption after oral administration". Additionally, FR '268 provides no teaching that opioid peptides, such as the opioid peptide according to the presently claimed invention, are included among the drugs used in the disclosed combinations.

In contrast, the presently claimed invention relates to inclusion complexes having a long duration of activity and improved efficacy having oral efficacy. In view of the Examiner's admission that the compositions of FR '268 are specifically designed to "avoid problems of poor absorption after oral administration", it is not even possible that FR '268 could have recognized the oral efficacy of the presently claimed inclusion complexes. Accordingly, the Examiner's arguments with respect to different motivation are moot in view of his admission that the cited reference teaches away from the presently claimed orally efficacious inclusion complexes.

Additionally, as presented above in section 1, the arguments of which are hereby incorporated by reference in their entirety, applicants have provided further data showing that the claimed opioid peptide to cyclodextrin derivative molar ratio of 1:5 to 2:1 is essential for the biological activity of the presently claimed inclusion complexes by the oral, rather than transcutaneous, route. This data shows that it would not at all have been obvious in view of the FR '263 and Nath et al. references that a cyclodextrin derivative enhances the stability, solubility, and bioavailability of opioid peptides delivered orally.

The opioid peptides included in the presently claimed inclusion complexes, then, are effective by oral administration, a significant improvement over the teachings of the FR '268 reference. The data in Tables 2 and 3 of the instant specification, at pages 14 and 15, further support this assertion by demonstrating that the presently claimed inclusion complexes are effective via oral administration. A person of ordinary skill in the art would have had no motivation to combine the references cited by the Examiner to arrive at the presently claimed invention as required by In re Fine in view of the fact that FR '268 teaches away from the presently claimed invention requiring a composition which is orally efficacious.

Regarding the Examiner's assertion that "the motivation used

to combine the two references is the desirability of forming a transcutaneously administrable composition comprising the compound of the Nath et al article", applicants respectfully reiterate that this combination is not the same as the presently claimed invention. In particular, the presently claimed invention relates to inclusion complexes which are orally efficacious. See claim 1. The combination suggested by the Examiner is transcutaneously administrable, but is not orally efficacious. Accordingly, the Examiner's proposed combination does not result in the same product as that which is presently claimed.

Accordingly, applicants respectfully submit that the presently claimed invention is unobvious over Nath et al. in view of FR '268 and respectfully request the Examiner to reconsider and withdraw the rejection of presently pending claims 1, 8-9, 11, and 15.

CONCLUSION

In light of the foregoing, applicants submit that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of all pending claims 1-6, 8-9, 11, and 14-15 and allow these claims. Favorable action with an early allowance of the claims is earnestly solicited.

Respectfully submitted,

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